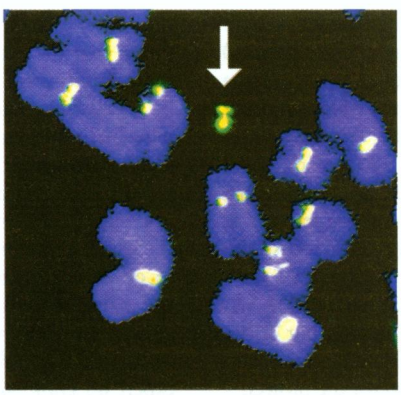
efforts aimed at protecting the natural habitat of the orangutan. Galdikas was instrumental in establishing the largest national park in Borneo, and she is involved with numerous conservation efforts in Indonesia. She has also been involved with the maintenance of a care center for orphaned orangutans and educational programs for children.

In the late 1950s, Schaller conducted the first scientific study of the mountain gorilla, and his book, *The Mountain Gorilla*, led to the establishment of the Virungas National Park in Rwanda. He has also studied tigers, lions, snow leopards, and pandas, and his books are known by field biologists around the world. As director of science for the Wildlife Conservation Society, Schaller has been a leading champion of conservation practices, and his efforts have led to the establishment of national parks in Brazil, East Africa, Mongolia, China, Tibet, and the United States.

## Fake DNA

The outlines of chromosome function have been clear for decades, but a new development—the creation of the first artificial human chromosome—gives scientists the tools to fill in the details. Reported by researchers at Cleveland's Case Western Reserve University School of Medicine in the April 1997 issue of *Nature Genetics*, the new chromosome should allow scientists to study gene expression and evolution, and will potentially improve gene therapy.

The finding also provides a model for studying environmental health, says Huntington F. Willard, a genetics professor and senior author on the study. For example, researchers can test how environmental agents cause chromosomes to malfunction during cell division and how toxins cause mutagenesis. Being able to work with an artificial human chromosome brings an experimental dimension to the Human Genome Project, says Willard, whose research has received funding from that project for several years.



John J. Harrington

**Small wonder.** The synthetic human microchromosome (beneath the arrow) created by investigators at Case Western Reserve University is surrounded by native human chromosomes. Fluorescent dyes cause chromosome material to appear blue while the centromeres appear green.

Artificial chromosomes could correct some defects in approaches to gene therapy as well, the authors contend. Current methods of gene therapy are hampered by unpredictable gene expression and vector shortcomings. For example, viral vectors can foster immune reactions, cause cell toxicity, and transfer only small amounts of genetic material. Available nonviral vectors do not segregate properly during repeated cell divisions.

"We decided the perfect vector would resemble a normal human chromosome," says John J. Harrington, the study's lead author and vice president of Athersys, a Cleveland, Ohio-based company that hopes to develop the new technology. "A micro version small enough to be manipulated and delivered to cells is the optimal way to go." Harrington looks toward a future where physicians can use ready-made chromosomes to treat a variety of genetic diseases.

But such applications are years away from use because of technical challenges, says Uta Francke, a genetics professor at the Stanford University School of Medicine and a member of a National Institutes of Health Panel to Assess the NIH Investment in Research on Gene Therapy, whose 1995 report called for better approaches to gene therapy. Still, Francke said of the new chromosomes, "The applications for biological research are very great."

To create the artificial chromosome, Case Western Reserve researchers pared its structure down to three essential components: centromeres, which guide chromosomes during cell division, telomeres, repeating DNA sequences that protect the ends of chromosomes and allow replication, and origins of replication, the sequences where DNA copying is begun. The scientists cloned centromere sequences consisting of repeats of alpha satellite DNA, huge arrays of a repeating 171 base-pair unit. Previous researchers had been unable to clone these large sequences, and had depended primarily on chopping up existing chromosomes rather than creating new ones. The team then added these centromere sequences, telomere sequences, and genomic DNA digested by enzymes to cultures of human sarcoma cells.

Cells absorbed the genetic material, assisted by positively charged lipids known to aid in DNA uptake. DNA-repair machinery within the cells apparently formed the material into chromosomes in three ways. Two involved hitching the DNA to existing chromosomes, which could disrupt genes. But other cells produced novel chromosomes that resembled naturally occurring ones but were 5–10 times smaller. These microchromosomes replicated normally through six months of mitotic cell division—about 240 generations.

Ethicists expressed optimism that microchromosomes might overcome some disadvantages of gene-therapy vectors, but cautioned that many of the same ethical questions remain. What are the risks of cancer and other side effects? Should adults make such treatment decisions for children? Should new genes be added to germ cells? In addition, questions arise about whether artificial chromosomes could be used to enhance traits such as intelligence, and how to address this possibility, says Michael H. Shapiro of the University of Southern California Law School in Los Angeles. "There are some very serious issues to be discussed," he says.

The Case Western Reserve team built on more than a decade of Willard's work, and on previous studies of yeast genetics. Yeast artificial chromosomes were developed in the early 1980s, and their use has offered insight into gene mapping, function, and identification. But larger, more complex human chromosomes had defied creation until now.

A first step in refining the discovery is ensuring that microchromosomes, not other genetic variants, are formed during the process, and that genes express reliably. Currently, the researchers are building microchromosomes in solution and inserting them into cells in culture to streamline the process. They're planning to inject microchromosomes into mice within the next six months.

The diseases likely to be attacked first with artificial human chromosomes are blood disorders, such as sickle cell anemia. Blood cells are easily removed from the body and reinserted after adding genetic material. Treating other genetic disorders, such as cystic fibrosis, awaits development of new methods for introducing microchromosomes into the body.

## A Known Human Carcinogen

A working group of the International Agency for Research on Cancer (IARC), located in Lyon, France, has stated that 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), the most toxic form of dioxin, is a known human carcinogen. Since 1987, the IARC has classified TCDD as a group B2, or "probable human," carcinogen.

George Lucier, chairman of the IARC dioxin working group, which released its reclassification of TCDD on 11 February 1997, said three lines of evidence were taken into account: animal studies, human epi-